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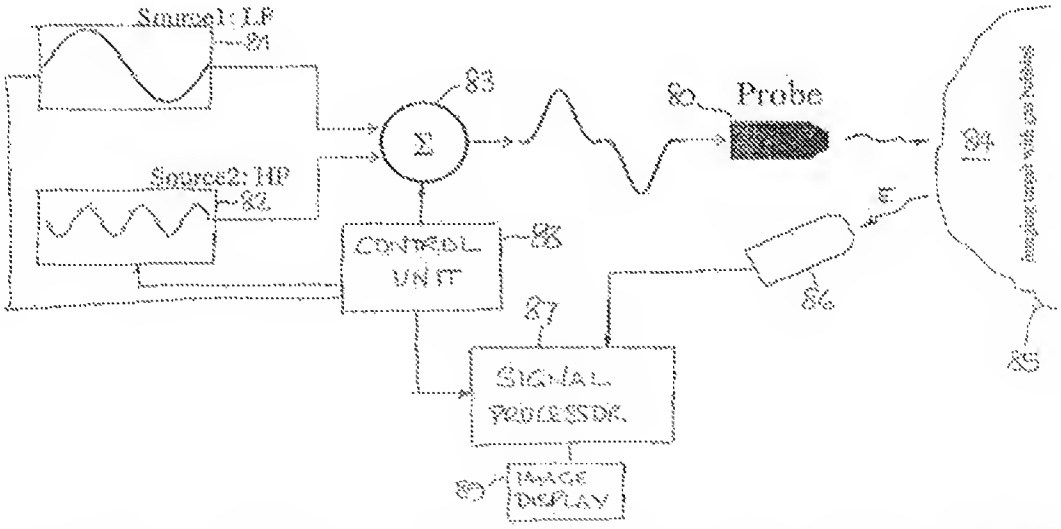
(54) Title: CONTRAST DUAL FREQUENCY IMAGING



(57) Abstract: A method and apparatus for ultrasound imaging which uses dual frequency excitation of a target. The target is simultaneously irradiated with a relatively low frequency ultrasound conditioning signal and a relatively high frequency ultrasound detection signal. The conditioning signal modulates a physical property (e.g. size) of first structures (e.g. gas bubbles) within the target, which modulation causes changes in the echo signal response of the first structures to the detection signal. A signal processor is adapted to process the received echo signals to detect the presence of the first structures by virtue of a first magnitude of detection signal echo arising from periods when the conditioning signal is in a first phase and a second, different, magnitude of detection signal echo arising from periods when the conditioning signal is in a second phase.

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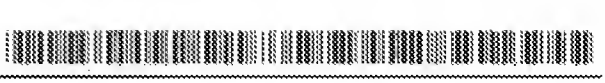

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CONTRAST DUAL FREQUENCY IMAGING

The present invention relates to ultrasound imaging techniques, and in particular to ultrasound imaging techniques that use contrast enhancement agents to enhance discrimination between different structures under examination within a target medium or body, e.g. tissues and other structures within the human body.

Over the past decade, contrast agent in a form of tiny gas bubbles has been introduced to improve image quality in ultrasound imaging techniques. The gas bubbles are infused into a region of interest to increase backscattered echoes from desired organs of interest. To extend the utility of ultrasound contrast imaging, research has been actively focused in developing efficacious ultrasound contrast agents and new contrast-specific imaging techniques.

Second harmonic-based techniques enhance the detection of ultrasound contrast agents within many structures, such as cardiac chambers. Second harmonic techniques exploit the differences in response of gas microbubbles and tissue to ultrasound irradiation. Soft tissues are known to be linear reflectors of ultrasound energy, whereas contrast bubbles exhibit a non-linear or harmonic behaviour when interacting with ultrasound waves.

By coincidence, it was found that imaging tissue at the second harmonic frequency, even without injection of contrast bubbles, improves image quality considerably. This mode, called native tissue harmonic imaging, has demonstrated advantages in various clinical applications.

However, recent studies have shown that imaging contrast bubbles and tissue at second harmonic frequency only is also associated with some disadvantages, such as harmonic contamination from tissue. Tissue harmonic contamination

reduces the contrast detection capability and therefore the contrast to tissue ratio. Higher harmonic frequencies were then suggested as a way to increase the ability to detect or discriminate between contrast gas bubbles and surrounding scattering medium and have shown promising *in vitro* and *in vivo* results, as described in Bouakaz *et al.*, Ultrasound in Medicine and Biology, Volume 28, Issue 1, pages 1–137 (January 2002).

It as an object of the present invention to provide an ultrasound imaging technique that is able to improve contrast bubble detection over existing techniques.

According to one aspect, the present invention provides an apparatus for ultrasound imaging comprising:

a signal generator;

a transmit transducer coupled to the signal generator for simultaneously irradiating a target with a relatively low frequency ultrasound conditioning signal and a relatively high frequency ultrasound detection signal;

a receive transducer for receiving echo signals from the irradiated target; and

a signal processor adapted to process the received echo signals to detect the presence of first structures within the target causing a first magnitude of detection signal echo arising from periods when the conditioning signal is in a first phase and a second, different, magnitude of detection signal echo arising from periods when the conditioning signal is in a second phase.

According to another aspect, the present invention provides an apparatus for ultrasound imaging comprising:

a signal generator;

a transmit transducer coupled to the signal generator for simultaneously irradiating a target with a relatively low frequency ultrasound conditioning signal and a relatively high frequency ultrasound detection signal;

a receive transducer for receiving echo signals from the target; and

a signal processor adapted to process the received echo signals to differentiate first structures within the target whose physical properties change as a function of the conditioning signal from second structures whose corresponding physical properties remain substantially invariant in response to the conditioning signal.

According to another aspect, the present invention provides a method of ultrasound imaging comprising the steps of:

simultaneously irradiating a target with a relatively low frequency ultrasound conditioning signal and a relatively high frequency ultrasound detection signal;

receiving echo signals from the target; and

processing the received echo signals to detect the presence of first structures within the target causing a first magnitude of detection signal echo arising from periods when the conditioning signal is in a first phase and a second, different, magnitude of detection signal echo arising from periods when the conditioning signal is in a second phase.

According to another aspect, the present invention provides a method of ultrasound imaging comprising the steps of:

simultaneously irradiating a target with a relatively low frequency ultrasound conditioning signal and a relatively high frequency ultrasound detection signal;

receiving echo signals from the target; and

processing the received echo signals to differentiate first structures within the target whose physical properties change as a function of the

conditioning signal from second structures whose corresponding physical properties remain substantially invariant in response to the conditioning signal.

Embodiments of the present invention will now be described by way of example and with reference to the accompanying drawings in which:

Figure 1 shows variation in a contrast agent bubble radius under insonification with a conditioning signal (the radius-time curve), for a bubble having nominal (resting) radius of 2 microns;

Figure 2 shows the echo signal response of a contrast agent bubble to a detection signal as a function of bubble size, for radius 1.85 microns (figure 2a) and radius 2.34 microns (figure 2b);

Figure 3 shows the echo signal response of a contrast agent bubble to an insonifying ultrasound beam having conditioning signal frequency of 0.5 MHz and detection signal frequency of 3.5 MHz;

Figure 4 shows the echo signal response of a contrast agent bubble to an insonifying ultrasound beam having conditioning signal frequency of 0.5 MHz and detection signal frequency of 3.5 MHz, the echo signal being filtered at the second harmonic of the detection signal frequency;

Figure 5 shows an optical image generated to determine the resting radius of a contrast agent bubble;

Figure 6 shows the variation in a contrast agent bubble diameter under insonification with a conditioning signal (the diameter-time curve) for the bubble of figure 5 having nominal (resting) diameter of 4 microns, as measured with an ultrafast camera;

Figure 7 shows filtered diameter-time curves for the bubble of figure 5, filtered at 0.5 MHz and 3.5 MHz;

Figure 8 shows a schematic diagram of exemplary insonifying apparatus;

Figure 9 shows first and second successive transmit waveforms used in a conventional pulse inversion imaging technique;

Figure 10 shows first and second successive transmit waveforms used in a pulse inversion conditioning and detection signal technique according to the present invention;

Figure 11 shows first and second echo signals from non-linear structures irradiated with the waveforms of figure 9;

Figure 12 shows first and second echo signals from non-linear structures irradiated with the waveforms of figure 10;

Figure 13 shows the sum of the echo signals of figure 11;

Figure 14 shows the sum of the echo signals of figure 12; and

Figure 15 shows a schematic diagram of an echo phase shift correlation process.

The method of the present invention is based on blending two frequency components for simultaneous transmission to irradiate or excite a region of interest of a target body under examination (generally described herein as a 'target'). A first, relatively low frequency component signal, referred to herein as the 'conditioning' or modulation signal, is combined with a second, relatively high frequency component signal, referred to herein as the 'detection' signal. The lower frequency (conditioning) signal is used to modulate the size of contrast agent bubbles by making them vibrate. The high frequency signal, which is blended with the low frequency signal, is used to interrogate the modulated bubbles, e.g. to enable imaging or detection by way of the local oscillations of the contrast agent bubbles that are induced by the low frequency signal.

An advantage of mixing the conditioning signal and the detection signal resides in the fact that the conditioning signal alters the physical properties of certain contrast agent structures (e.g. gas bubbles). An important physical property of the gas bubbles that is modulated by the conditioning signal is size, and therefore also resonant frequency. The size of a gas bubble therefore varies

according to the compression and rarefaction caused by the acoustic pressure applied by the conditioning signal. The size of a gas bubble will reach a minimum during the positive pressure cycle of the conditioning signal and a maximum during the negative pressure cycle of the conditioning signal. In other words, the bubble size will oscillate, expanding in the negative (rarefaction) phase of the conditioning signal and shrinking in the positive (compression) phase of the conditioning signal.

During these two phases of the conditioning signal, the detection signal is transmitted and used to detect or image the same bubbles. Hence, the detection signal will sense the same bubbles but at two different stages: small and large size depending on the phase of the low frequency signal. During the expansion phase (rarefaction of the lower frequency signal), larger bubbles are insonified with the higher frequency detection signal, and during the shrinkage phase (compression of the lower frequency signal), smaller bubbles are insonified with the higher frequency detection signal. Consequently the response of the gas bubbles to the detection signal will be different in the positive and negative cycles of the conditioning signal.

When non-oscillating scatterers (such as body tissue) are present (no gas bubbles present in the target medium), the response will be identical in both phases of the conditioning signal since these scatterers do not oscillate. This finding will increase the distinction in response between gas bubbles and tissue, usually termed contrast agent to tissue ratio compared to other existing methods.

With reference to figure 8, to deploy such a method, an ultrasonic array transducer or 'probe' 80 is used that is able to transmit both the higher and lower frequency components. Such a requirement can be fulfilled with, for example, the dual frequency transducer described in Bouakaz *et al.*, Ultrasound

in Medicine and Biology, Volume 28, Issue 1, pages 1–137 (January 2002). The dual frequency transducer described therein contains two different types of active elements that are sensitive at two distinct frequency bands. Other types of transducer probe may be used, as will be apparent to the person skilled in the art.

The transducer 80 is connected to a signal generator comprising first and second signal sources 81, 82 and a signal blender 83 for summing or otherwise combining the relatively low frequency conditioning signal from source 81 and the relatively high frequency detection signal from source 82. The blended or combined signal is supplied to the transducer 80 which irradiates a region of interest or target 84 in a body 85 under examination.

The target 84 includes different types of structure that are capable of being resolved and separately imaged using the effects of the transmitted ultrasound signals. The target preferably includes at least: (i) a first type of structure that has at least one physical property which varies as a function of the conditioning signal; and (ii) a second type of structure for which the corresponding physical property does not vary significantly as a function of the conditioning signal.

In preferred applications, the first type of structure is a contrast agent, such as fluid or fluid-filled 'bubbles', which produce a non-linear response to the ultrasonic excitation. Preferably, the bubbles are gas bubbles as well known in the art of ultrasound imaging.

In preferred applications, the second type of structure is body tissue which produces a substantially linear response to the ultrasonic excitation. It will be understood that the response of the first and second types of structure may be dependent upon the frequency and / or intensity of ultrasonic excitation, and

therefore suitable such parameters for the ultrasonic excitation may be selected accordingly.

The contrast agent may be introduced into the target body using known techniques that cause the contrast agent to selectively locate at selected locations in the target.

A receive transducer 86 is used to receive echo signals 'E' from the target 84, which echo signals are passed to a signal processor 87. The signal processor 87 is adapted to process the received echo signals E to differentiate between first structures within the target whose physical properties change as a function of the conditioning signal and the second structures whose corresponding physical properties remain substantially invariant in response to the conditioning signal. Various techniques that may be used by the signal processor 87 will be discussed hereinafter.

A control unit 88 may be provided to coordinate and synchronise the activities of the signal generator components 81, 82, 83 and the signal processor 88. Those skilled in the art will recognise that the functions of the transmit and receive transducers 80, 86 may be combined in a single transducer or transducer array.

Preferably, the system includes an image display unit 89 adapted for the display of the first and / or second structures and their relative locations within the target body, according to known principles of ultrasound imaging. Alternatively, or in addition, the image display unit could include any suitable form of output device, including a data storage receptacle.

As used in the present specification, the expressions 'imaging' and 'detection' in the context of the transmitted and received ultrasound signals is intended to

encompass the obtaining of any kind of location data relating to specific structures within the target 84.

Referring now to figure 1, the radius-time curve 10 is shown for a vibrating contrast agent bubble that is being insonified with 0.5 MHz signal having an acoustic amplitude of 180 kPa. This low frequency signal is used as a conditioning signal (produced by signal source 81, figure 8). The bubble has a resting or nominal radius of 2 microns as indicated by the flat portion 11 of the curve. The bubble is encapsulated by a shell whose elastic properties are similar to those of known, available contrast agents. The bubble expands and compresses under the influence of the conditioning signal. It reaches a maximum radius of 2.34 microns (reference numeral 12) during the expansion phase and shrinks to a minimum radius of 1.85 micron (reference numeral 13) during the compression phase.

A higher frequency detection signal, generated by signal source 82 is then used to image the oscillations of this bubble at its maximal and minimal size. Figure 2(a) shows the response 20 of the small (1.85 micron) bubble, and figure 2(b) shows the response 25 of the large bubble, to a 3.5 MHz detection signal with an acoustic amplitude of 120 kPa. Since the smallest bubble has a natural resonance frequency closer to the detection signal frequency (3.5 MHz), its acoustic response demonstrates much higher amplitude 21 than that of the larger bubble (shown at 26). In addition, the smaller bubble clearly demonstrates more non-linearity in the response.

Figure 3 shows the response 30 of the bubble having nominal 2 micron radius to an excitation signal that contains dual frequencies 0.5 MHz and 3.5 MHz (simultaneous transmission). The dotted line 31 represents the radius-time curve (shown as a function of change in radius) of the bubble to the signal having only a single frequency 0.5 MHz. This shows the expansion phase

(positive-going portion 32) and the compression phase (negative-going portion 33) of this bubble relative to the nominal radius (zero portion 34). The solid line 35 shows the acoustic response at 3.5 MHz, which indicates a strong asymmetry.

The bubble exhibits a stronger response during the compression phase 33, which corresponds to the smaller bubble radius (down to 1.85 microns). During the expansion phase 31, where the original bubble grows to up to 2.34 microns, the bubble response is weaker. Figure 3 demonstrates that the bubble response is different depending on the phase of the conditioning 0.5 MHz signal. During the compression phase of the 0.5 MHz signal, the bubble shrinks and gets smaller. At this time the detection signal at 3.5 MHz will detect or image a small bubble. At the rarefaction phase of the 0.5 MHz signal, the bubble expands and the detection signal will detect a different bubble with much larger size.

Thus, in a general sense, it will be noted that the detection signal echoes have a first average magnitude (relatively large) arising from periods (e.g. 33) when the conditioning signal is in a first (compression) phase and a second average magnitude (relatively smaller) arising from periods (e.g. 32) when the conditioning signal is in a second (expansion) phase.

Figure 4 shows the same results but with these, the echo signals 40 are filtered around the second harmonic frequency (7.0 MHz). The dotted line 41 represents the radius-time curve (change in radius) indicating the response of the bubble to the 0.5 MHz signal. The solid line 42 shows the second harmonic (2H) echo signal. When the bubble is smaller and closer to resonance size (negative-going portion 43), it generates more non-linearities and thus more of the second harmonic component compared to when it expands (positive-going

portion 44) and the non-linear behaviour of the bubble is damped. The dotted line 41 is the same as line 31 in figure 3.

Ultra-fast optical observations of bubbles insonified simultaneously at two different frequencies were carried out using an ultra-fast camera. To interrogate the bubbles at two different frequencies, two different transducers were used. The transducers had centre frequencies of 0.5 MHz and 3.5 MHz. The transducers were mounted in a Plexiglas container and positioned such that their focal distances coincided at a depth of 75 mm. The optical observations were carried out at a frame rate of 13.45 million frames per second and 128 successive frames were recorded. The acoustic pressures as measured separately were approximately 100 kPa at both the 0.5 MHz and 3.5 MHz frequencies. Commercially available contrast agent was used.

Figure 5 shows the first frame 50, which was recorded at the arrival of the ultrasound signal. Bubbles with various sizes were present in the view and the following analysis was based on the bubble 51 which had a resting diameter of approximately 4 microns.

Figure 6 shows the global diameter-time curve 60 of that bubble 51, which was oscillating under the effects of both 0.5 MHz conditioning signal and 3.5 MHz detection signal. The curve 60 shows clearly two frequencies present in the bubble response, a low frequency indicated by period 61 and a higher frequency indicated by period 62. Figure 7 shows the filtered diameter-time curves 71, 72 around 0.5 MHz (dotted line 71) and 3.5 MHz (solid line 72) frequencies.

Up to 3 microseconds (period indicated at 73), the 0.5 MHz signal amplitude is low and the vibrations of the bubble 51 during this period of time are weak. In addition, the compression and expansion phases of the bubble are small

meaning that the bubble size does not change significantly between the compression and rarefaction phases 74, 75. Consequently the vibrations 72 of the bubble at 3.5 MHz are almost equal between the two phases 74, 75. However beyond 3 microseconds, the 0.5 MHz signal amplitude has increased and much stronger vibrations of the bubble now occur at this frequency. The bubble 51 radius decreases to about 3 microns and expands up to 6 microns. During these oscillations, the 3.5 MHz detection signal interrogates the same bubble 51 of variable size. This is seen in the response 72 at 3.5 MHz, which shows different responses depending whether a compression phase (period shown at 76) or an expansion phase (period shown at 77) of the 0.5 MHz conditioning signal is seen by the bubble.

It will be understood that selection of appropriate conditioning signal frequencies and intensities and selection of appropriate detection signal frequencies and intensities will be dependent upon the physical properties of the body under examination and of the first and second types of structures therein.

In a typical application of imaging human or animal tissue, in which conventional, commercially available contrast agents are used, the preferred conditioning signal frequency lies in the range 10 kHz to 5 MHz. More preferably, the conditioning signal frequency lies in the range 100 kHz to 800 kHz. The detection signal frequency preferably lies in the range 1 MHz to 50 MHz, and more preferably lies in the range 1 MHz to 5 MHz.

The signal blender 83 for combining the conditioning and detection signals may use simple signal summation, mixing, amplitude or power modulation techniques.

Signal processing of the echo signals in the signal processor 87 to detect the differences between the positive and negative phases of the conditioning signal can be performed using a number of techniques. These include pulse inversion, Doppler or correlation methods as will now be described.

Pulse inversion, Doppler or correlation methods can all be applied to: (i) the full echo response; (ii) the second harmonic of the echo; (iii) higher harmonics or sub-harmonics of the echo. Depending upon the exact nature of the body under examination, different degrees of discrimination between the first and second types of structure within the target may be achieved.

With reference to figures 9 to 14, the use of a pulse inversion technique for signal processing will now be described. Figure 9 shows first and second pulses 90, 91 for insonification of the target 84 according to known techniques. The target 84 is excited using a first transmit signal pulse 90 followed by a second transmit signal pulse 91 that is inverted (180 degree phase shifted). In figure 9, the first and second pulses each comprise an envelope of effectively a single frequency. In the present invention, the same pulse inversion sequence is used, but in this case transmit pulses 100, 101 essentially each comprise a blended signal comprising two frequencies: the conditioning signal and the detection signal.

Figure 11 shows first and second echo signal pulses 110, 111 resulting from the first and second excitation signal pulses 90, 91. Figure 12 shows the first and second echo signal pulses 120, 121 resulting from the first and second blended excitation signal pulses 100, 101. It is immediately clear that the difference between the first and second echo signals 120, 121 is substantially larger than the difference between the first and second echo signals 110, 111, illustrating the substantial improvement in discrimination possible with the present invention.

The echoes from the pulse inversion process are summed according to known techniques and the results shown in figures 13 and 14.

Figure 13 shows the echo summation (difference signal) 130 for the conventional process, indicating only small differences between the first and second (inverted) echo signals. This difference represents second (and/or higher harmonic components that are not cancelled by the summation process. In case of a fully linear system, the summation would be zero.

Figure 14 shows the analogous result 140 for the double frequency imaging (conditioning signal frequency plus detection signal frequency) technique of the present invention. The echo difference signal 140 resulting from the summation is significantly stronger than the echo difference signal 130 from simple pulse inversion. For the case of a linear system, the summation will result in a doubling of the scattered power in the echo difference signal.

In producing a second (inverted) excitation signal 101, the phase inversion may be applied to the lower frequency conditioning signal, to the higher frequency detection signal, or to both.

An alternative signal processing technique is to obtain a correlation between identical first and second signals time shifted relative to one another.

Figure 15 shows a first dual frequency transmit signal pulse 150 (e.g. of N periods of the conditioning signal frequency) and a second dual frequency transmit signal pulse 151 which is replica of the first, but shifted by a half period of the conditioning signal frequency.

Two segments 152, 153 of the same length are then selected from the two echoes corresponding to the response to the expansion pressure cycle and to the compression pressure cycle. These two segments 152, 153 of the echo signal pulses are then correlated or compared. The resulting correlation is maximal when no bubbles (non-linear structures) are present (only tissue, or linear structures) meaning that the response at the compression and expansion phases are similar. The correlation is null (or very small) when bubbles (i.e. non-linear structures) are present in the body being examined.

These two implementation options can be performed on the whole received echo signals – meaning the raw echo signal is used to perform the summation (figure 14) or delay and correlation (figure 15). The signal processing can also be carried out on filtered echo signals. A second harmonic filter can be applied to the echo signals in either of the figure 14 and figure 15 techniques.

A super-harmonic filter (third harmonic, fourth harmonic, fifth harmonic or a combination thereof) can also be used prior to carrying out the signal processing described above. A sub-harmonic filter and or an ultra-harmonic filter could also be used.

Other embodiments are intentionally within the scope of the accompanying claims.

CLAIMS

1. Apparatus for ultrasound imaging comprising:

a signal generator;

a transmit transducer coupled to the signal generator for simultaneously irradiating a target with a relatively low frequency ultrasound conditioning signal and a relatively high frequency ultrasound detection signal;

a receive transducer for receiving echo signals from the target; and

a signal processor adapted to process the received echo signals to detect the presence of first structures within the target causing a first magnitude of detection signal echo arising from periods when the conditioning signal is in a first phase and a second, different, magnitude of detection signal echo arising from periods when the conditioning signal is in a second phase.

2. The apparatus of claim 1 in which the signal processor is adapted to process the received echo signals so as to differentiate said first structures within the target whose physical properties change as a function of the conditioning signal from second structures whose corresponding physical properties remain substantially invariant in response to the conditioning signal.

3. The apparatus of claim 1 or claim 2 in which the conditioning signal has a frequency in the range 10 kHz to 5 MHz.

4. The apparatus of claim 3 in which the conditioning signal has a frequency in the range 100 kHz to 800 kHz.

5. The apparatus of any one of claims 1 to 4 in which the detection signal has a frequency in the range 1 MHz to 50 MHz.

6. The apparatus of claim 5 in which the detection signal has a frequency in the range 1 MHz to 5 MHz.

7. The apparatus of any one of claims 1 to 6 in which the signal processor is adapted to determine the response of the first structures to the detection signal during positive and negative cycles of the conditioning signal.

8. The apparatus of any one of claims 1 to 6 in which the signal generator and transmit transducer are adapted to produce a first excitation signal pulse and successively a second excitation signal pulse that is a phase-inverted replica of the first excitation signal pulse; and

in which the signal processor includes means for processing the received echo signals to determine the response of the first structures to the first and second excitation signal pulses.

9. The apparatus of claim 8 in which the first and second excitation signal pulses comprise the conditioning signal.

10. The apparatus of claim 8 or claim 9 in which the first and second excitation signal pulses comprise the detection signal.

11. The apparatus of any preceding claim in which the transmit transducer is adapted to transmit at least a first excitation pulse and a second excitation pulse each including a said conditioning signal frequency and a said detection signal frequency, the second excitation pulse being a phase inversion of the first excitation pulse; and

in which the signal processor comprises a pulse inversion processor for determining a difference between an echo signal from the first excitation pulse and an echo signal from the second excitation pulse.

12. The apparatus of any one of claims 1 to 10 in which the transmit transducer is adapted to transmit at least a first excitation pulse and a second excitation pulse each including a said conditioning signal frequency and a said detection signal frequency, the second excitation pulse being a phase shifted version of the first excitation pulse; and

in which the signal processor comprises a correlation processor for determining a difference between at least portions of an echo signal from the first excitation pulse and an echo signal from the second excitation pulse.

13. The apparatus of any preceding claim further including an image display system adapted to indicate locations of the first structures within the target.

14. The apparatus of claim 2 further including an image display system adapted to indicate relative locations of the first and second structures within the target.

15. The apparatus of any preceding claim in which the signal processor is adapted to process one or more harmonics of the received echo signal.

16. A method of ultrasound imaging comprising the steps of:

simultaneously irradiating a target with a relatively low frequency ultrasound conditioning signal and a relatively high frequency ultrasound detection signal;

receiving echo signals from the target; and

processing the received echo signals to detect the presence of first structures within the target causing a first magnitude of detection signal echo arising from periods when the conditioning signal is in a first phase and a second, different, magnitude of detection signal echo arising from periods when the conditioning signal is in a second phase.

17. The method of claim 16 wherein the step of processing the received echo signals is adapted to differentiate said first structures within the target whose physical properties change as a function of the conditioning signal from second structures whose corresponding physical properties remain substantially invariant in response to the conditioning signal.

18. The method of claim 16 or claim 17 in which the first structures are contrast agent structures, and including the step of introducing the contrast agent structures into selected locations of the target.

19. The method of claim 18 in which the contrast agent structures are bubbles of fluid.

20. The method of claim 19 in which the contrast agent structures are bubbles of gas.

21. The method of any one of claims 16 to 20 in which the physical property of the first structures that changes in response to the conditioning signal is a size of each of the first structures.

22. The method of claim 21 when dependent from claim 18 or claim 19 in which a physical property of the first structures that changes in response to the conditioning signal is a resonant frequency.

23. The method of any one of claims 16 to 22 in which the conditioning signal has a frequency in the range 10 kHz to 5 MHz.

24. The method of claim 22 in which the conditioning signal has a frequency in the range 100 kHz to 800 kHz.

25. The method of any one of claims 16 to 24 in which the detection signal has a frequency in the range 1 MHz to 50 MHz.

26. The method of claim 25 in which the detection signal has a frequency in the range 1 MHz to 5 MHz.

27. The method of any one of claims 16 to 26 in which the step of processing the received echo signals comprises the step of determining the response of the first structures to positive and negative cycles of the conditioning signal.

28. The method of any one of claims 16 to 26 in which the step of processing the received echo signals comprises the step of determining the response of the first structures to a first excitation signal pulse and to a successive second excitation signal pulse that is a phase-inverted replica of the first excitation signal pulse.

29. The method of claim 28 in which the first and second excitation signal pulses comprise the conditioning signal.

30. The method of claim 28 or claim 29 in which the first and second excitation signal pulses comprise the detection signal.

31. Apparatus substantially as described herein with reference to the accompanying drawings.

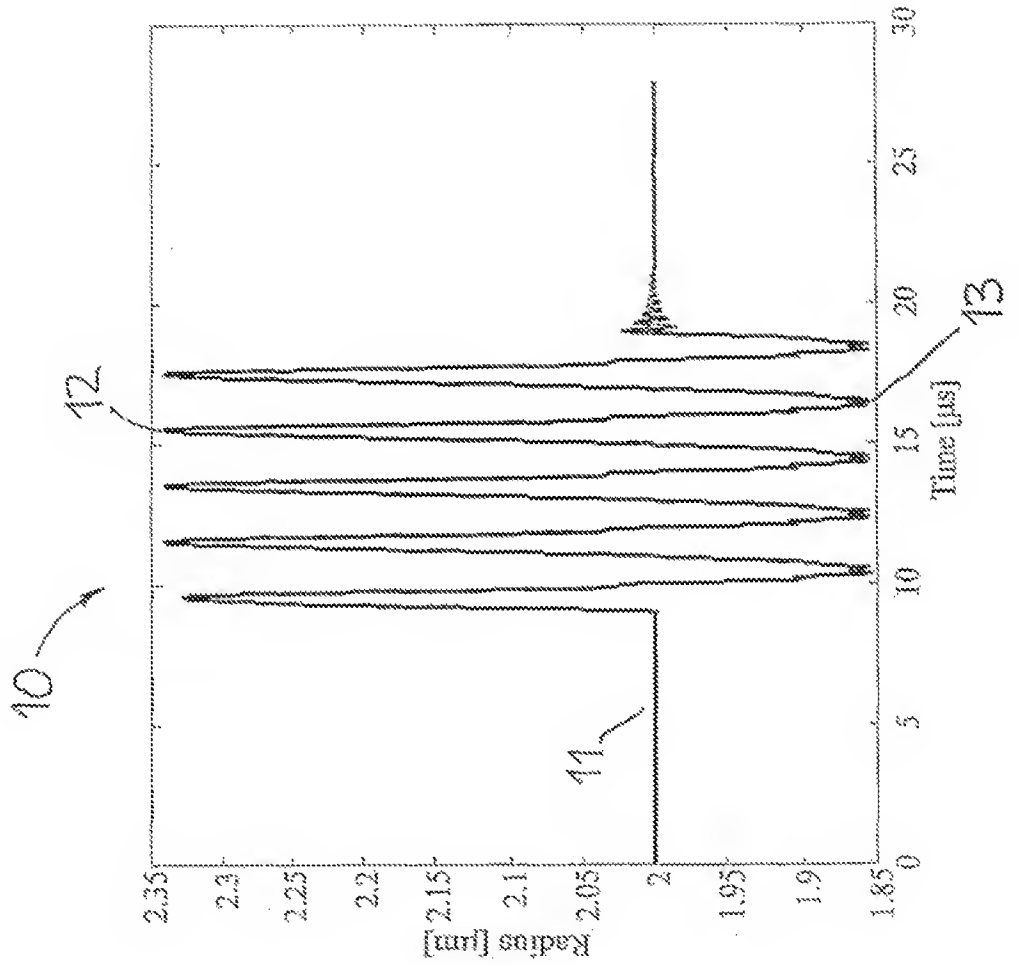
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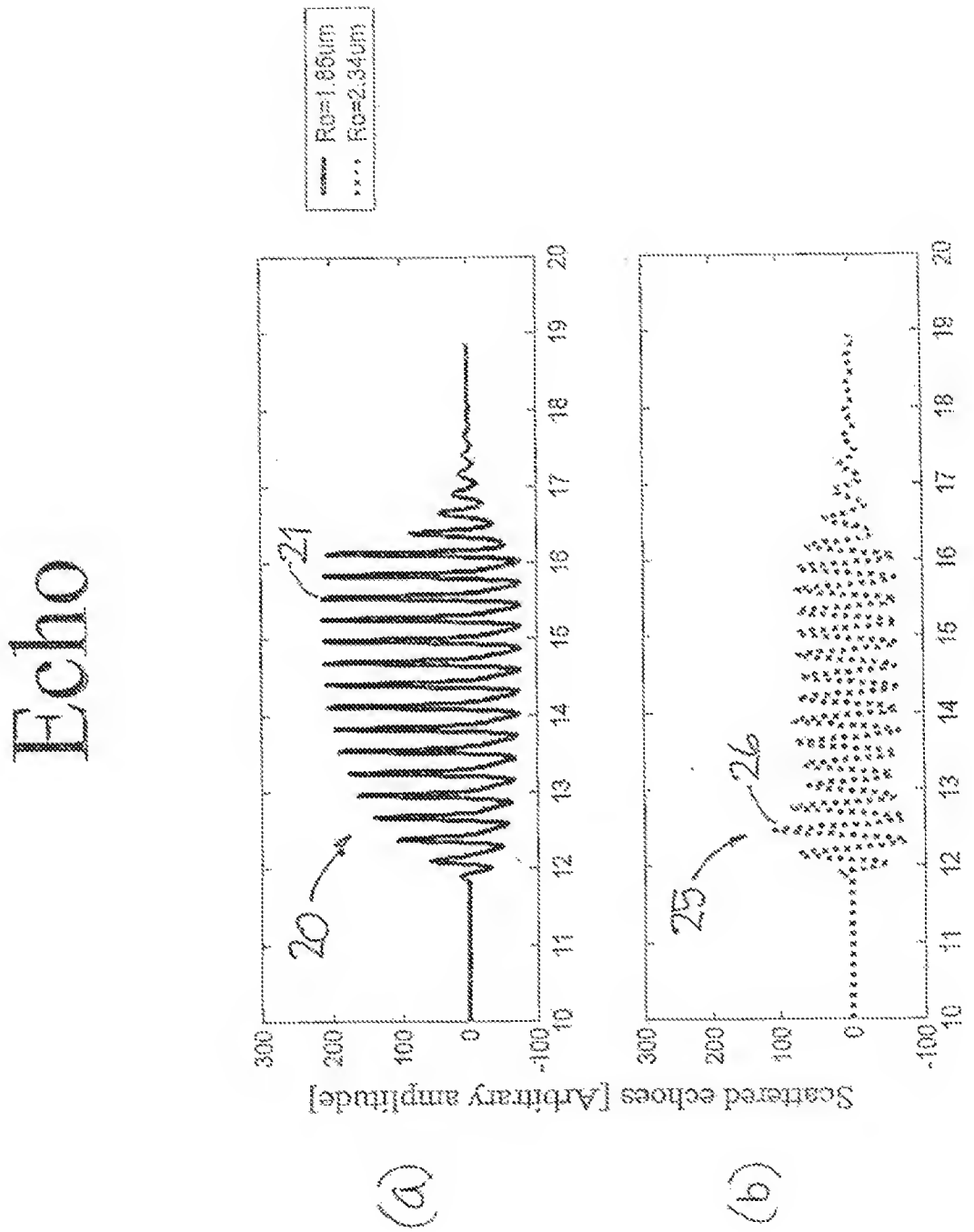
Fig. 1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20
21
25
26
Scattered echoes [Arbitrary amplitude]
300
200
100
0
-100
10
11
12
13
14
15
16
17
18
19
20

Fig. 2

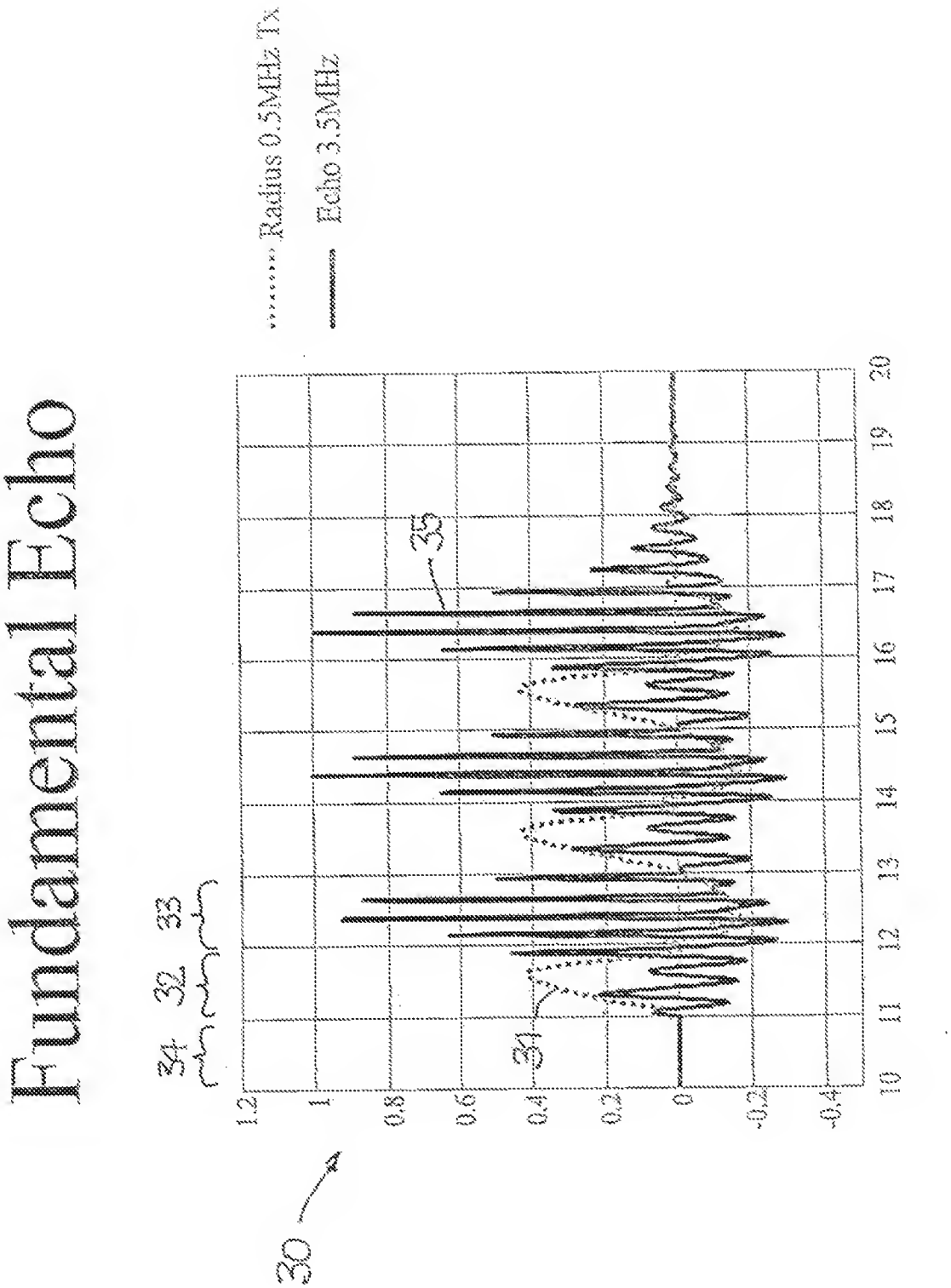

Fundamental Echo
Radius 0.5MHz Tx
Echo 3.5MHz
30
31
32
33
34
35
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
10
11
12
13
14
15
16
17
18
19
20

Fig. 3

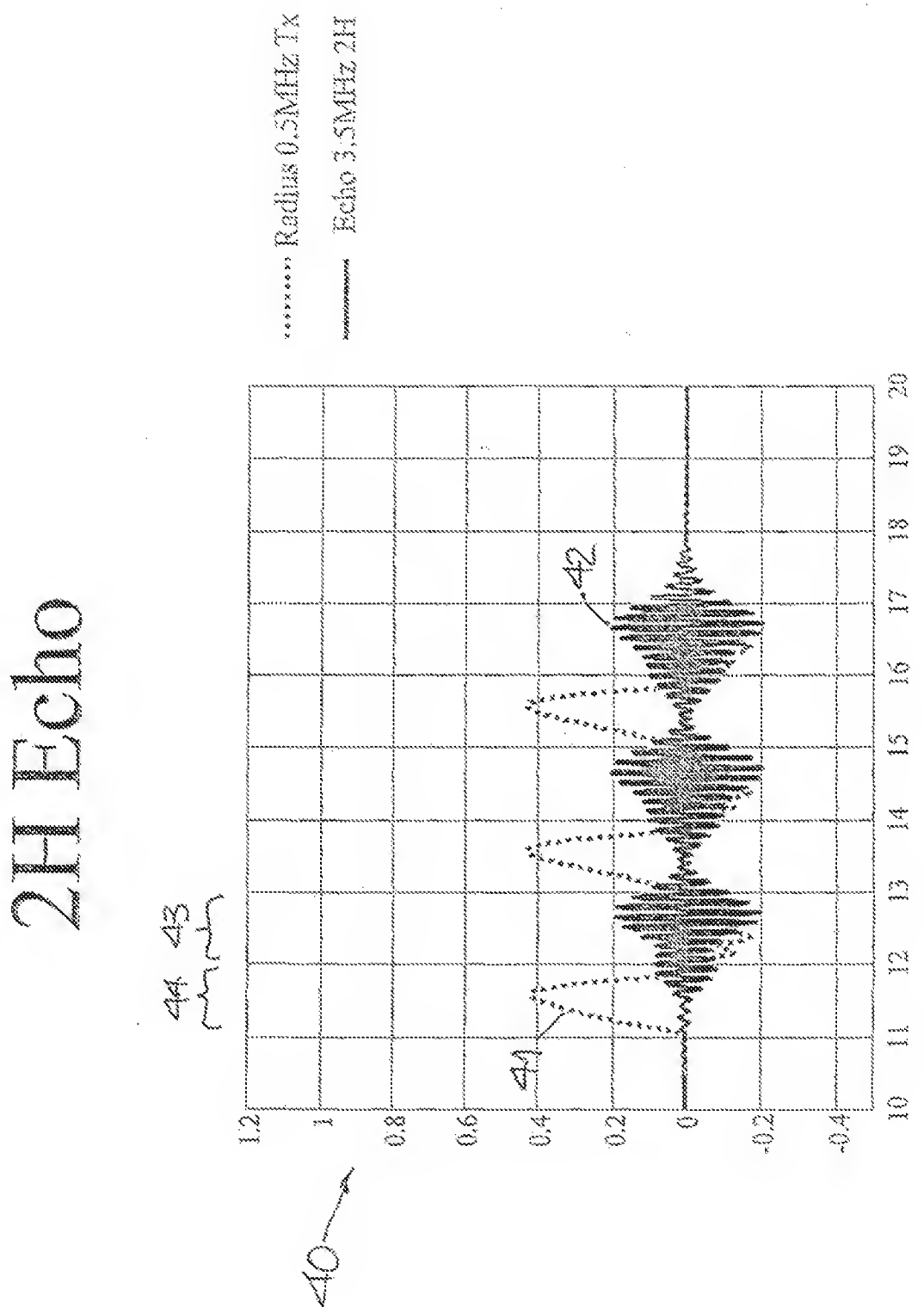
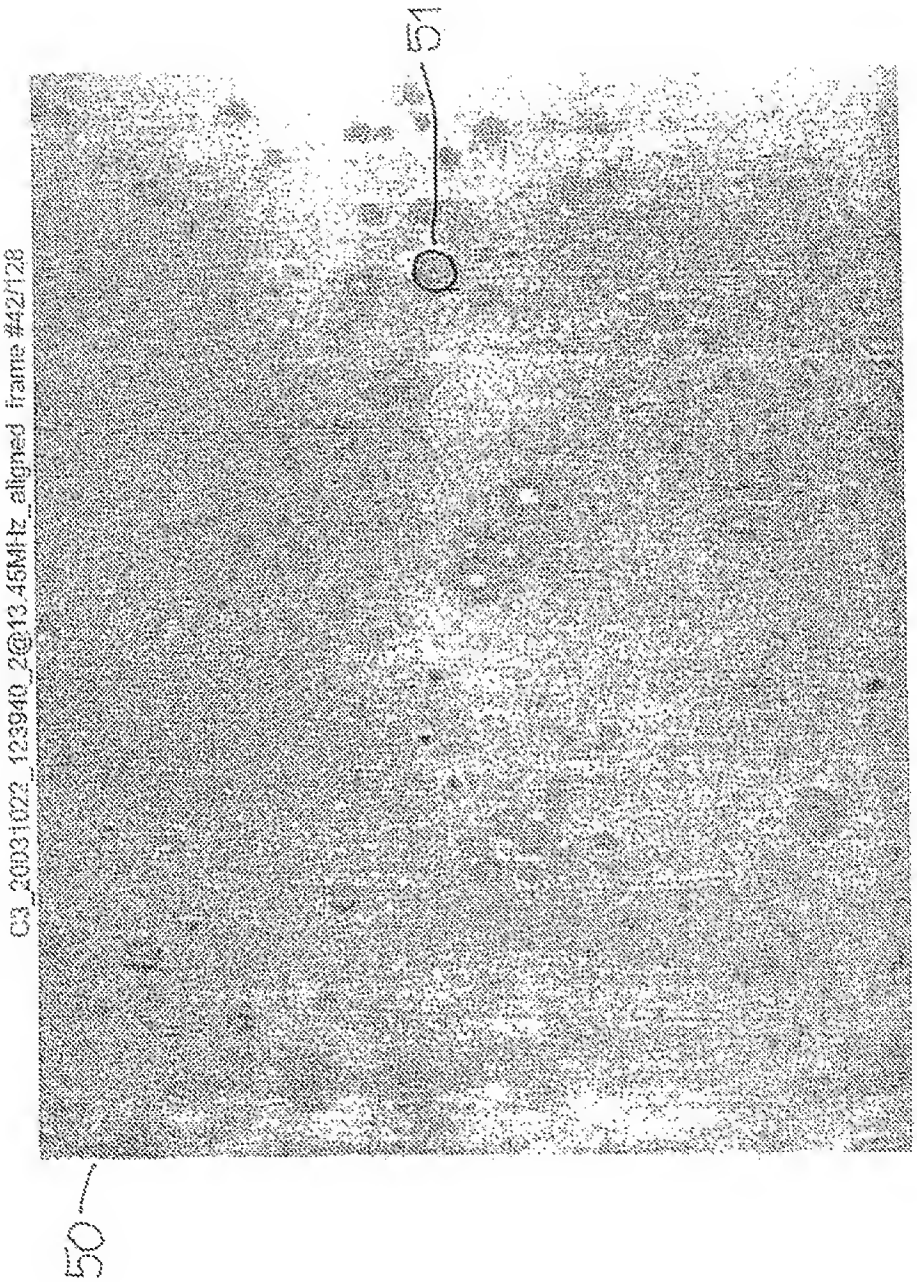

2H Echo
Radius 0.5MHz Tx
Echo 3.5MHz 2H
40
41
42
43
44
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
10
11
12
13
14
15
16
17
18
19
20

Fig. 4

Fig. 5



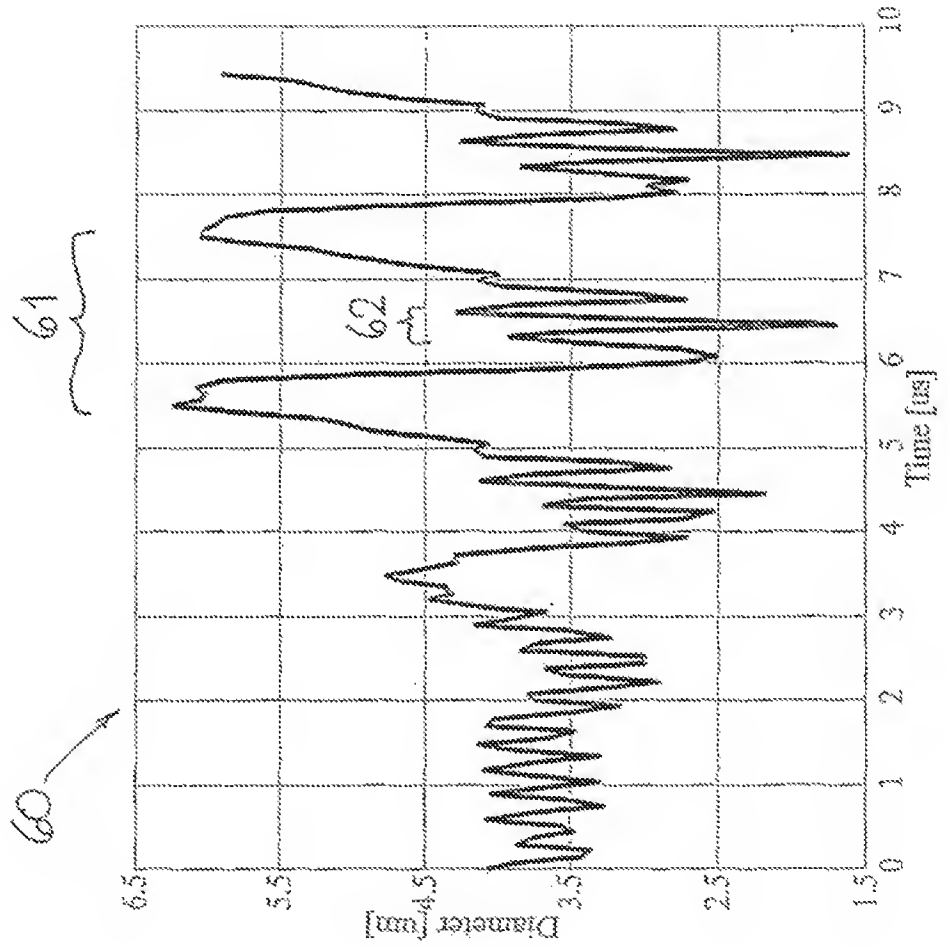


Fig. 6

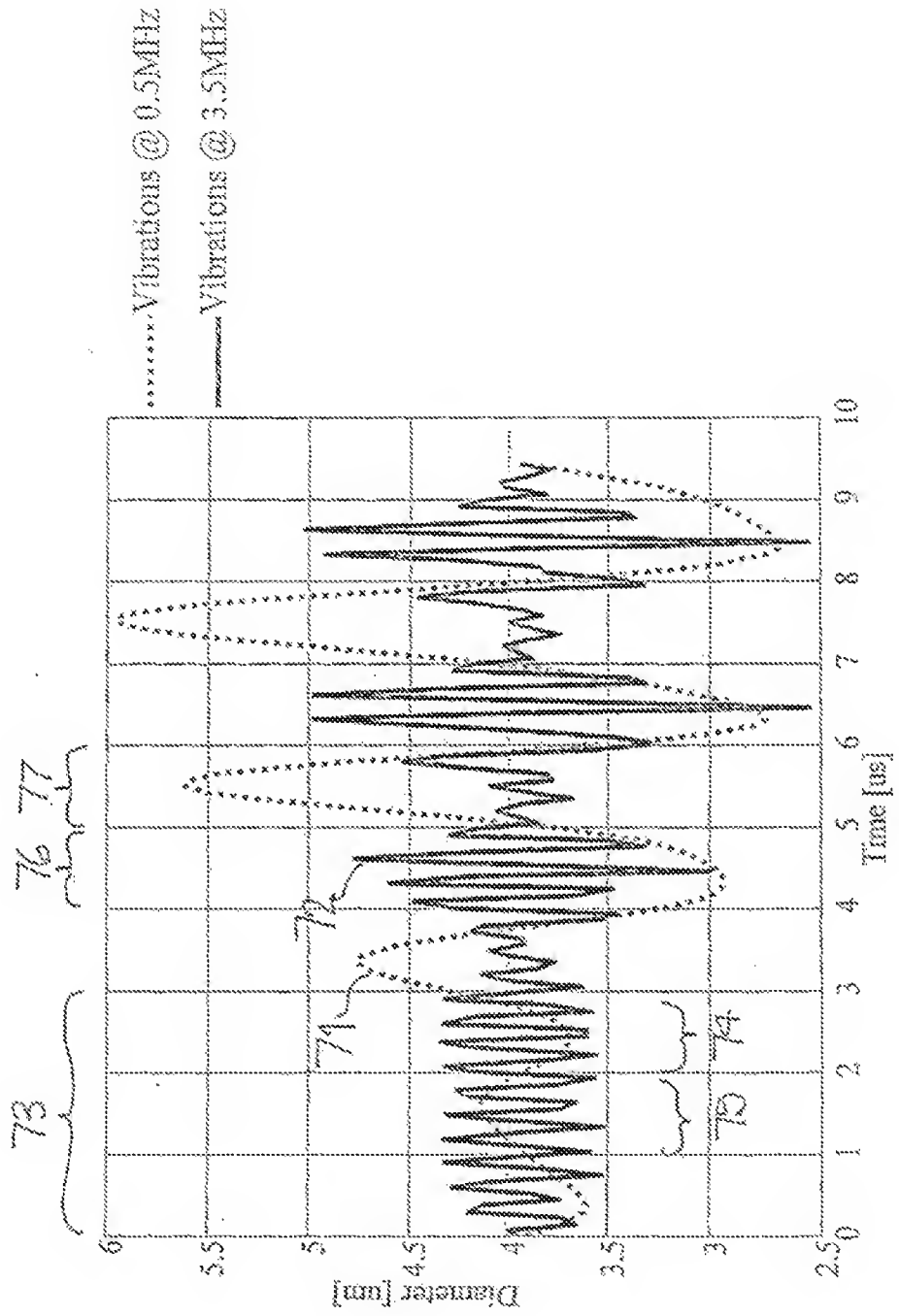

Vibrations @ 0.5MHz
Vibrations @ 3.5MHz
Diameter [um]
Time [us]
6
3.5
5
4.5
4
3.5
3
2.5
0
1
2
3
4
5
6
7
8
9
10
71
72
73
74
75
76
77

Fig. 7

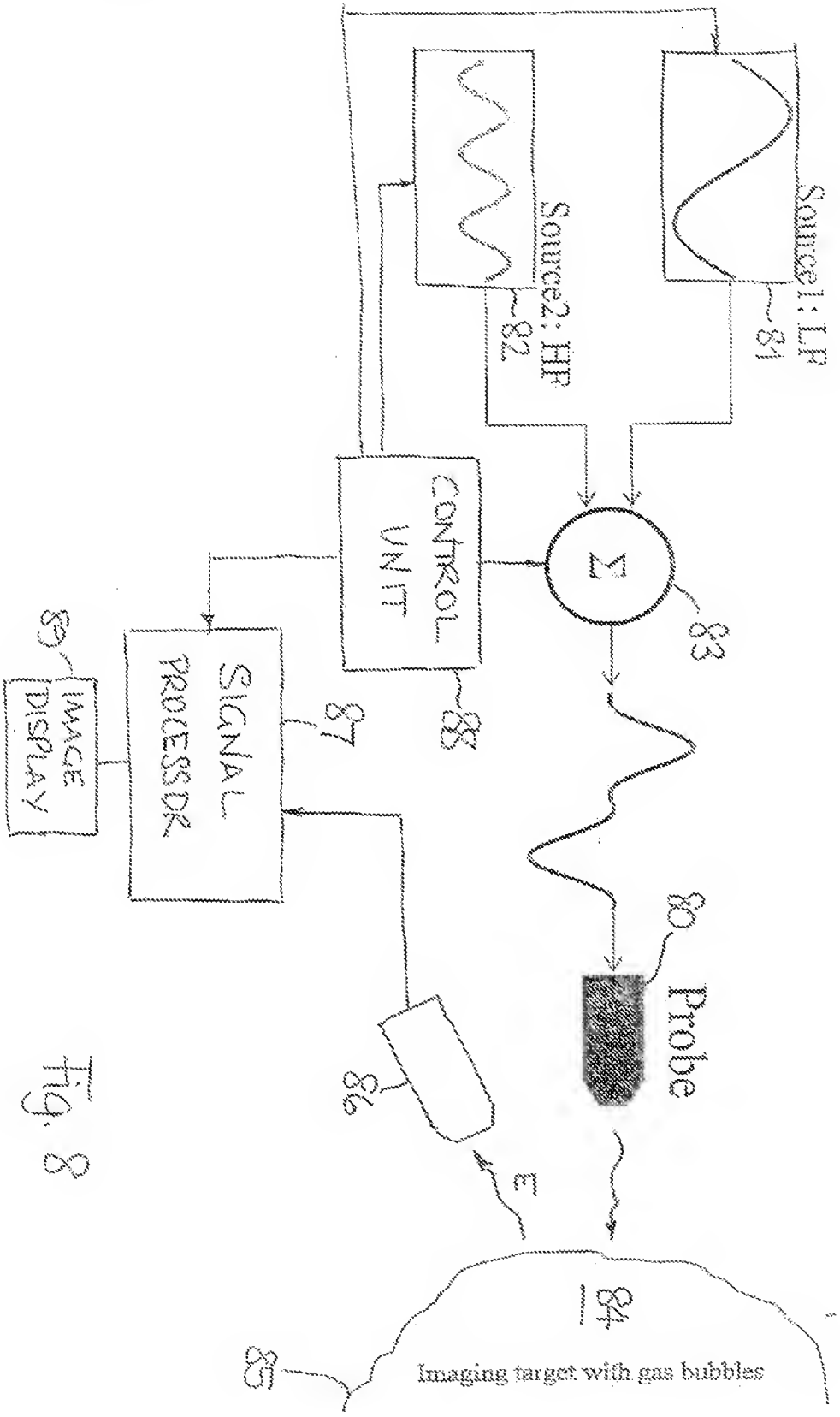

Source1: LP
81
Source2: HP
82
CONTROL UNIT
M
83
SIGNAL PROCESSOR
87
88
IMAGE DISPLAY
89
80 Probe
86
E
84
Imaging target with gas bubbles
85

Fig. 8

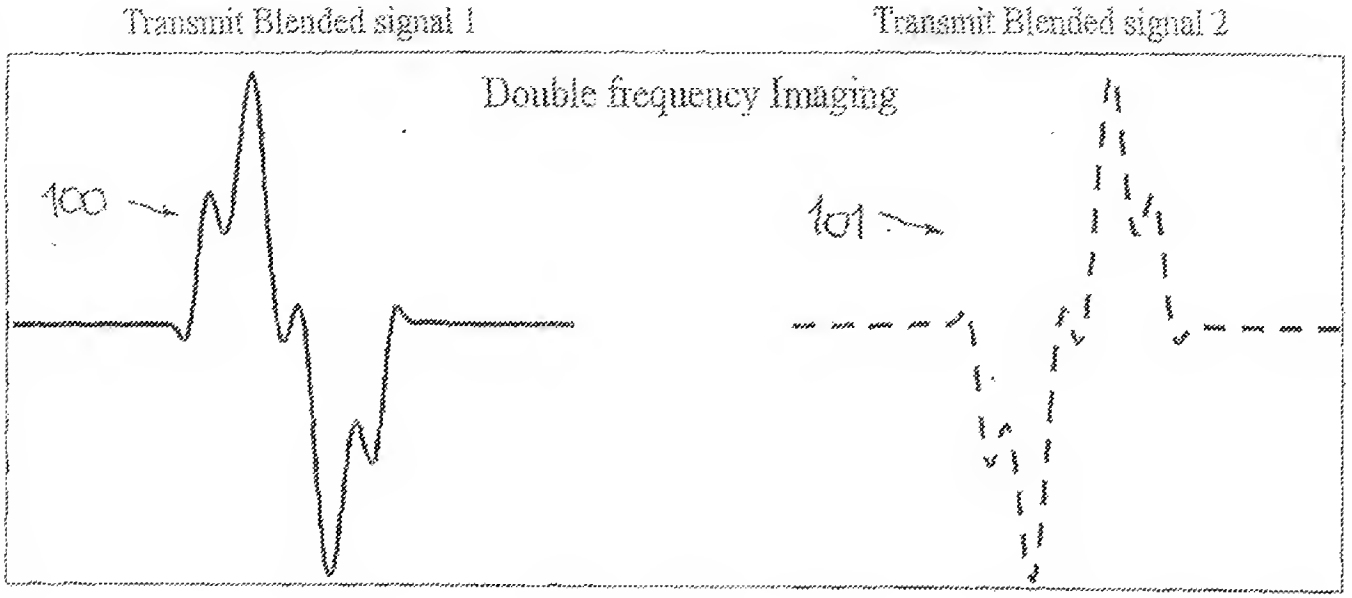

Option1
Transmit Blended signal 1
Transmit Blended signal 2
Double frequency Imaging
100
101

Fig. 10

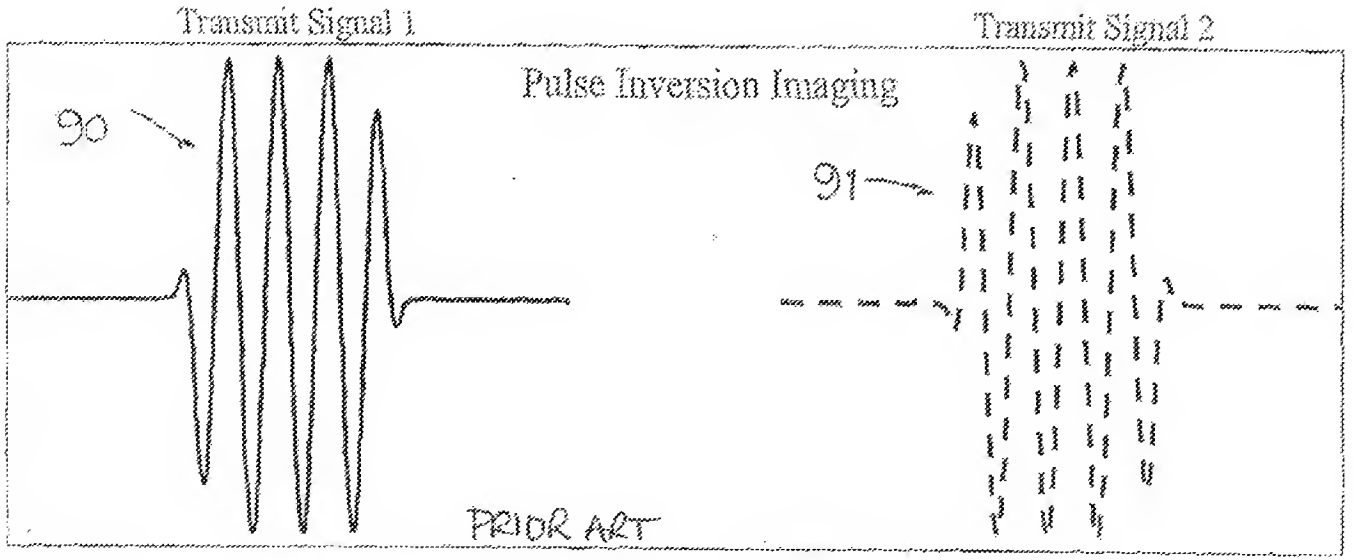
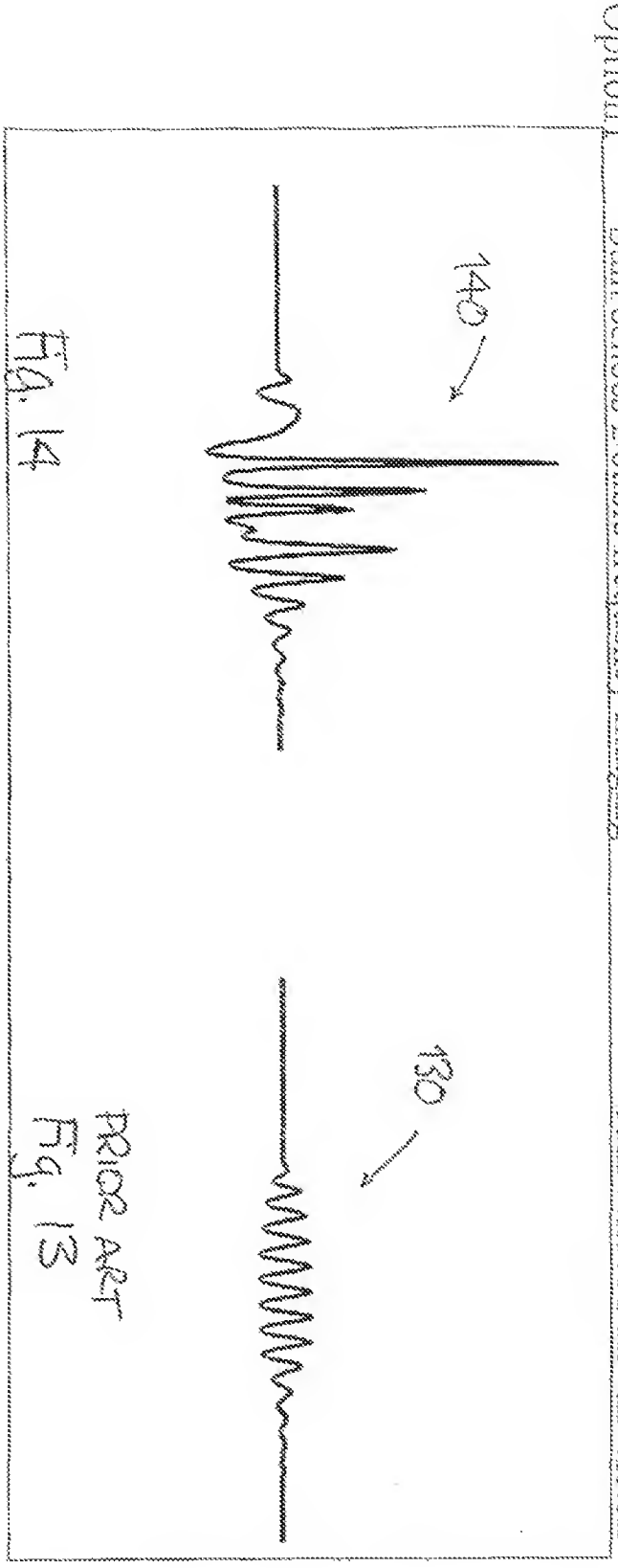

Transmit Signal 1
Transmit Signal 2
Pulse Inversion Imaging
90
91
PRIOR ART

FIG. 9

FIG. 12

PRIOR ART

FIG. 11



PRIOR ART
Fig. 13

Fig. 14

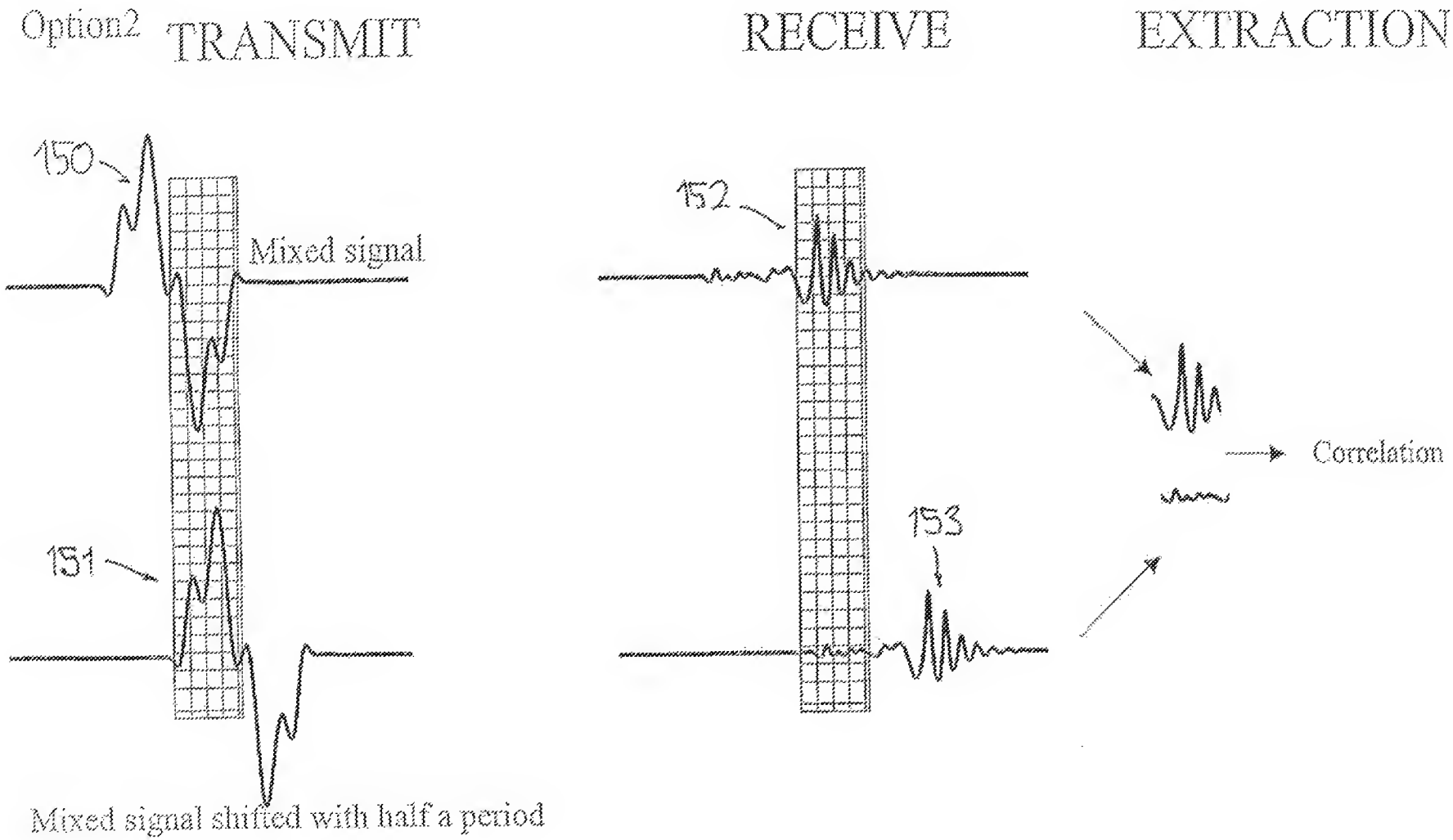

Option2
TRANSMIT
RECEIVE
EXTRACTION
150
Mixed signal
151
Mixed signal shifted with half a period
152
153
Correlation

FIG. 15

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/000668

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01S15/89

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01S

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 312 383 B1 (LIZZI FREDERIC LOUIS ET AL) 6 November 2001 (2001-11-06)	1-7,13, 14, 16-27,31
Y	abstract; figures 1,5A-5D column 5, line 10 - column 7, line 15	8-12,15, 28-30
Y	US 6 371 917 B1 (FERRARA KATHERINE W ET AL) 16 April 2002 (2002-04-16) column 2, line 7 - line 23 column 4, line 24 - column 7, line 9 column 9, line 26 - column 10, line 47	8-12,15, 28-30
A	US 6 629 449 B1 (KLINE-SCHODER ROBERT ET AL) 7 October 2003 (2003-10-07) abstract; figures 1-3 column 9, line 11 - line 37 column 12, line 4 - column 13, line 30	1,16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 May 2005	01/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Niemeijer, R

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/000668

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6312383 B1	06-11-2001	US 6186951 B1	13-02-2001
		US 2001001108 A1	10-05-2001
US 6371917 B1	16-04-2002	AU 9375198 A	27-04-1999
		CA 2304273 A1	15-04-1999
		EP 1019093 A1	19-07-2000
		JP 2001518360 T	16-10-2001
		WO 9917808 A1	15-04-1999
US 6629449 B1	07-10-2003	US 6408679 B1	25-06-2002
		US 6457346 B1	01-10-2002
		US 6467331 B1	22-10-2002
		US 6463785 B1	15-10-2002